IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Erion *et al.*	
Serial No.: 09/518,501	Group Art Unit: 1624
Filed: March 3, 2000	Examiner: McKenzie, T.
Title: NOVEL PHOSPHORUS-CONTAINING PRODRUGS	

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Commissioner for Patents
Washington, D.C. 20231

DECLARATION OF MARK D. ERION
PURSUANT TO 37 C.F.R. § 1.132

I, Mark D. Erion, a citizen of the United States, declare and say that:

1. I have a Ph.D. in synthetic organic chemistry from Cornell University, and I have over 16 years experience in the pharmaceutical industry. I am currently the Executive Vice President of Research & Development at Metabasis Therapeutics, Inc. in San Diego, CA. As such, I am responsible for all discovery research and development. I am an inventor of the HepDirect™ prodrug technology, a platform technology useful for targeting drugs to the liver. I also headed the R&D team responsible for the identification of clinical candidates for diabetes, hepatitis B, and hepatocellular carcinoma. Prior to my being a co-founder of Metabasis Therapeutics in 1997, I was the Division Vice President of Research at Gensia, Inc. in San Diego, CA. Prior to joining Gensia in 1991, I was a group leader at Ciba-Geigy where I directed a team in the area of protein engineering at Ciba-Geigy's Central Research Laboratories in Switzerland. I have over 80 publications and 25 U.S. patents. Through my work, I have had extensive experience in the area of prodrugs, including the invention of the HepDirect™ prodrug technology.

2. I am an inventor of the above-referenced application for the patent filed on March 3, 2000. I have reviewed the specification, the pending claims, and the office action mailed July 15, 2002.

CERTIFICATE OF MAILING
(37 C.F.R. §1.8a)

I hereby certify that this paper (along with anything referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as First Class Mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

1/15/2003
Date of Deposit

Jill C. Youkel
Name of Person Mailing Paper

Jill C. Youkel
Signature of Person Mailing Paper

2. I am an inventor of the above-referenced application for the patent filed on March 3, 2000. I have reviewed the specification, the pending claims, and the office action mailed July 15, 2002.

3. It is my understanding that the Examiner has found that claims 1-18, 20-46, 48-57, 150-157, 165-166, and 171-173 are indefinite and not enabled because of the use of the term "prodrug." In particular, it is my understanding that the Examiner finds the structures of the claimed prodrugs to be uncertain. The Examiner believes that one can not determine what compounds are claimed.

4. Contrary to the Examiner's position, a person of ordinary skill in the art can readily determine what is or what is not a prodrug of the current invention. The tests for making such determinations are routine and well-known in the art. As defined at p. 15 of the specification a prodrug is a compound that undergoes a chemical modification to form a biologically active molecule or a precursor to the biologically active drug. There are many commonly known prodrugs. For example, a compound may have a free hydroxyl group on it. A common prodrug of a hydroxyl is an ester. Esters are often quickly broken down within the body to produce the compound with the free hydroxyl. In this example, the ester is the prodrug. In general, each functional group, *e.g.* hydroxyl, thiol, amine, carboxylic acid, has a set of well described prodrugs that have proven useful for masking the functional group in a manner that enables improved oral bioavailability, improved pharmacokinetics, improved distribution, or other properties readily observable during testing in animals and man. It is well recognized that based on the functional group and the reasons for using a prodrug, one skilled in the art can usually choose a prodrug strategy that is usually successful without undue experimentation.

5. The tests for whether a compound is or is not a prodrug are routine, do not require undue experimentation, and were well-known in the art as of March 1999. Typically prodrugs are evaluated by first establishing assays that monitor production of the biologically active drug. This is typically accomplished using HPLC or HPLC coupled with mass spectroscopy. All techniques are routine for pharmaceutical companies and do not comprise undue experimentation. For example, if one wanted to determine if a compound was a prodrug of this invention, they could look for the compound's activation as in Examples C or D in the specification at pp.116-118. Example C and D describe the process of determining the activation of phosphoramidate prodrugs by rat liver microsomes and human microsomes. The prodrugs are converted into MPO_2-(NHR^{6-}). The specification describes how HPLC techniques can be used to quantify the formation of MPO_2-(NHR^{6-}). The specification also describes an alternative technique where the conversion of the prodrug can be monitored by the depletion of NADPH, an essential cofactor in the reaction. NADPH is easily measured spectrophotometrically. In addition, Example G, at pp. 119-120, describes the process of determining the activation of antiviral phosphoramidate prodrugs by monitoring the intracellular generation of the corresponding nucleoside triphosphates in isolated rat hepatocytes. The metabolites were easily detected by uv absorption at 254 nm.

6. In some cases, the mechanism for activation of the prodrug is well understood making it even easier to test for conversion to the biologically active drug. For instance, an article in *Pharm. Res.* (Exhibit 1) reveals that concentrations of the prodrug bis(POM)-PMEA and its metabolites mono(POM)-PMEA and PMEA were determined using a reversed-phase HPLC method. The activation of the prodrug was confirmed by incubating the prodrug with carboxylesterase.

7. In addition to these analytical methods, prodrugs that are converted to the biologically active drug are readily evaluated by using *in vitro* or *in vivo* assays to demonstrate a biological response. As described in Example I (pp. 120-121), prodrugs are readily shown to be converted to the biologically active drug by monitoring glucose production in primary rat hepatocytes. Inhibition of glucose production occurs following prodrug conversion, since the prodrug itself is not an FBPase inhibitor nor an inhibitor of gluconeogenesis

8. I also note that the specification provides adequate detail to a person of ordinary skill in the art in order to allow them to prepare the prodrugs of the current invention. A person of ordinary skill in the art could routinely prepare prodrugs of the invention particularly in view of the general procedures for prodrug preparation given at pp. 89-95 of the specification and by the definition of the term "prodrug" at p. 15 of the specification.

9. In view of the specification, a person of ordinary skill in the art can readily determine what is or what is not a prodrug of this invention.

Jan. 14, 2003
Date

Mark D. Erion, Ph.D.